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Biomarkers to predict and track diseases

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Biomarkers are fast becoming an essential part of clinical research. A biomarker must be an indicator of disease that can be measured accurately, easily, and cheaply, preferably with non-invasive techniques. Ideally, the biomarker is associated with the disease and its functional effect on the patient. In this issue of *The Lancet Neurology*, Tabrizi and co-workers¹ provide an exemplary model of the use of biomarkers in HD research.

Although Huntington's disease (HD) has been recognised as a neurological disorder since 1872, our understanding of its pathogenesis and course has burgeoned only recently. Since 2000, the number of publications on HD has increased fourfold. And clinical research in HD has witnessed three main paradigm shifts.

First, the dominant genetic transmission of HD provides a unique opportunity to study apparently healthy individuals before the disease manifests. The emphasis of clinical research has shifted to the study of what is now referred to as the "prodrome" of HD, because by the time a conventional clinical diagnosis of HD is given, imaging and pathological research has shown that substantial cell death has already occurred.^{2,3} Many studies have shown that cognitive, sensory, motor, psychiatric, and neuroimaging findings are evident at least 15 years before a conventional motor diagnosis.^{4–7} Given that previous reports have suggested that death occurs about 15 years after a conventional motor diagnosis of HD,⁸ the research window for HD has at least doubled, resulting in a disease duration of about 30 years.

Second, a revised appreciation of neuroimaging, physiological, and pathological findings suggest that the emphasis on changes in the basal ganglia and its connections is restrictive. Although the most pronounced findings might occur in the striatum, key changes in the brain also include thinning (and possible thickening) of the cortical ribbon, early morphological changes in other brain structures, various findings in white matter, and early dysfunction in structurally spared brain regions.⁹ In light of these findings, the research emphasis has also shifted towards the study of the whole brain, which capitalises on methodological advances in studying the morphology, neurochemistry, metabolic, and functional capacities of several brain systems.

Third, the HD field is forging new standards to aid more rapid scientific advancements through multinational multidisciplinary, collaborative research models. Specialists in many distinct fields are converging to advance knowledge at a rapid pace. Collaborations among pharmaceutical and biotech companies, government organisations, private and public academia, as well as lay organisations, have changed the face of research. For example, consortia, or working groups, are being established across organisational boundaries to decide on how to expedite progress (eg, the European Huntington's Disease Network, the Huntington Society of Canada, the Huntington Study Group, and the International

The author is the principal investigator of the PREDICT-HD study.

Huntington Association). Single-site, single-investigator studies are hindered by slow recruitment and their emphasis on one clinical research hypothesis, whereas multi-site, multi-investigator studies are able to capitalise on shared recruitment resources and the acquisition of cross-specialty data that might advance healthcare practices in the near future.

TRACK-HD is a multinational, multispecialty, longitudinal observational study of 120 clinically premanifest HD gene carriers, 123 patients with early-stage HD, and 123 controls. Although the current publication is the first from this group, its contributions are many.

The TRACK-HD study reports the replication of clinical and biological markers that were previously suggested in the PREDICT-HD study. More specifically, TRACK-HD supports the findings that brain volumes,¹⁰ the generation of precisely timed responses,¹¹ smell identification,⁵ irritability,¹² and emotion recognition¹³ are among the earliest indicators of HD and are detectable years, if not decades, before a conventional diagnosis.^{4,5,7} Moreover, TRACK-HD builds on what has been learnt from PREDICT-HD; namely, that some measures are sensitive to disease effects across the disease spectrum, spanning from health to different stages of clinical impairment. The TRACK-HD finding that the measures of caudate volume, the ability to generate timed responses, and irritability remain good markers of disease in patients with HD after conventional clinical diagnosis is key to the future design of clinical trials. Further analyses of this rich dataset are sure to aid the selection of the best biomarkers to use in experimental therapeutics, depending on the stage of HD.

Additionally, the TRACK-HD research group is to be lauded for the expediency with which their recruitment and baseline data were acquired. With the high cost of clinical trials and the known rate-limiting factor of slow recruitment, the recruitment of 366 participants in 8 months is an achievement that future researchers can emulate and aspire to.

Finally, the methods of transparency shown in this report are noteworthy, and the inclusion of the supplementary data as electronic media can also do much to advance research progress. For example, TRACK-HD has more missing data for emotional recognition, apathy, and cortical thickness than it does for other measures. The reasons cited for the missing data are disease related (ie, some measures are acquired best during early rather than late stages of the disease) and site specific. The reasons for site effects vary, however, and can have a profound effect on the design of future clinical trials. Crucially, biomarkers will need to be validated across cultures, languages, and education levels.

Biomarker research follows a similar pipeline to drug research: from discovery, through initial documentation, exploratory use in the prodrome and manifest disease stages, to publication and regulatory approval, and ideally onward to widespread adoption in the clinics. The TRACK-HD and PREDICT-HD studies provide examples of worldwide collaboration that begins to address some components of this pipeline. Much further work is welcome from these groups, as well as others, to advance biomarkers for HD and for other neurodegenerative diseases.

References

1. Tabrizi S, Langbehn DR, Leavitt BR, et al. Biological and clinical manifestations of Huntington's disease in the TRACK-HD study: cross-sectional analysis of baseline data. *Lancet Neurol*. 2009 published online July 30. 10.1016/S1474-4422(09)70170-X
2. Aylward EH. Change in MRI striatal volumes as a biomarker in preclinical Huntington's disease. *Brain Res Bull*. 2007; 72:152–58. [PubMed: 17352939]
3. Gomez-Tortosa E, MacDonald ME, Friend JC, et al. Quantitative neuropathological changes in presymptomatic Huntington's disease. *Ann Neurol*. 2001; 49:29–34. [PubMed: 11198293]

4. Paulsen JS, Magnotta VA, Mikos AE, et al. Brain structure in preclinical Huntington's disease. *Biol Psychiatry*. 2006; 59:57–63. [PubMed: 16112655]
5. Paulsen JS, Langbehn DR, Stout JC, et al. Detection of Huntington's disease decades before diagnosis: the Predict-HD study. *J Neurol Neurosurg Psychiatry*. 2008; 79:874–80. [PubMed: 18096682]
6. Paulsen JS. Functional imaging in Huntington's disease. *Exp Neurol*. 2009; 216:272–77. [PubMed: 19171138]
7. Paulsen JS, Hayden M, Stout JC, et al. Preparing for preventive clinical trials: the PREDICT-HD study. *Arch Neurol*. 2006; 63:883–90. [PubMed: 16769871]
8. Gusella JF, McNeil S, Persichetti F, et al. Huntington's disease. *Cold Spring Harb Symp Quant Biol*. 1996; 61:615–26. [PubMed: 9246488]
9. Weaver, K.; Williams, A.; Konopa, P.; Aylward, E. Neuroimaging in Huntington's Disease. In: Leavitt, BR., editor. *Huntington's Dementia*. 1. Lake Worth, FL: Carma Publishing LLC; 2008. p. 32
10. Nopoulos P, Magnotta VA, Mikos A, Paulson H, Andreasen NC, Paulsen JS. Morphology of the cerebral cortex in preclinical Huntington's disease. *Am J Psychiatry*. 2007; 164:1428–34. [PubMed: 17728429]
11. Zimelman JL, Paulsen JS, Mikos A, Reynolds NC, Hoffmann RG, Rao SM. fMRI detection of early neural dysfunction in preclinical Huntington's disease. *J Int Neuropsychol Soc*. 2007; 13:758–69. [PubMed: 17697407]
12. Duff K, Paulsen JS, Beglinger LJ, Langbehn DR, Stout JC. Psychiatric symptoms in Huntington's disease before diagnosis: the PREDICT-HD study. *Biol Psychiatry*. 2007; 62:1341–46. [PubMed: 17481592]
13. Johnson SA, Stout JC, Solomon AC, et al. Beyond disgust: impaired recognition of negative emotions prior to diagnosis in Huntington's disease. *Brain*. 2007; 130:1732–44. [PubMed: 17584778]

Figure 1.
Immunofluorescent light micrograph showing accumulation of mutant huntingtin (red) in a cell from the striatum